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Green synthesis of silver nanoparticles using Teucrium polium leaf extract and assessment of their antitumor effects against MNK45 human gastric cancer cell line

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ABSTRACT

The development of simple, cost effective, biocompatible, eco-friendly and scalable techniques for synthesis of nanomaterials is one of the most important fields of research in nanoscience. Silver nanoparticles (AgNPs) are one of the most frequently used nanomaterials in industrial and biomedical fields due to their chemical stability, good biocompatibility, anti-microbial and anticancer properties, high electrical conductivity, and great optical properties. In the present study, we developed an eco-friendly method to produce stable silver nanoparticles using the leaf extract of a medicinal plant of *Teucrium polium* (T. polium). The green synthesized silver nanoparticles (T. polium-AgNPs) were characterized by UV–**V**isible spectroscopy, X-ray diffraction (XRD) study, fourier transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM). The biosynthesized nanoparticles exhibited significant anticancer activity against MNK45 human gastric cancer cell line. The data obtained in the study shows the potent therapeutic value of T. polium-AgNPs and the scope for further development of anticancer drugs.

1. Introduction

In recent years metallic nanoparticles and carbon based nanomaterials have gained much attention as a new anticancer agents for cancer therapy. Carbon based nanostructures such as carbon nanotubes, graphene oxide, fullerenes, and specially graphene quantum dots widely used as drug delivery vehicles, imaging and photothermal agents for treatment of cancer [1–5]. Metallic nanomaterial like gold, silver, iron, cooper and zinc oxide NPs reported to play a powerful role in cancer therapy providing better targeting, drug delivery and gene silencing [6]. Among the metallic nanomaterials, silver nanoparticles (AgNPs) are much more popular in the fields of medicine, cosmetic, pharmaceutical products, food industry, electronics, agriculture antimicrobial agent, cosmetic and paints [1,7,8]. In medical field, AgNPs have been extensively used for diagnostic, drug delivery and tissue engineering, due to their unique physicochemical and optoelectronic properties, **low** cost method for fabrication, ease of synthesis, characterization and surface modification in the nanoscale range [8,9]. Recent efforts showed the potential of the AgNPs for utilization as anti-angiogenic, antimicrobial, anti-viral, antioxidant, and anticancer agents [1,10]. Generally, silver nanoparticles are synthesized by a variety of chemical and physical approaches such as laser ablation [11], laser irradiation [12], chemical reduction [13], ultraviolet (UV) irradiation [14], and thermal decomposition [15]. Although these conventional routes to produce nanoparticles are effective, most of them are very expensive and in most cases, the surface passivator or capping reagents are needed to prevent nanoparticles from aggregation. Unfortunately many organic passivators such as marcapto acetate, thiourea, thiophenol, etc. Are toxic enough to cause environment pollution if large scale NPs are produced [16]. Recently biosynthetic methods using natural resources such as plants, microorganisms, algae, marine organisms, have emerged as a simple alternative to noxious chemical or physical methods [17]. Bioactive molecules present in natural plant extracts such as proteins, peptides, polysaccharides, phenolics, enzymes, and vitamins acts as both reducing and capping agent for ecofriendly synthesis of

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silver NPs, without using any harmful chemical compounds [18].

Gastric (stomach) cancer, a multifactorial, heterogeneous, and aggressive disease is the fourth most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide. Its treat is difficult, primarily because most patients present advanced stages of the diseases upon the initial time of diagnosis [19]. Treatment for gastric cancer typically includes surgical removal of the tumor and lymph nodes near the cancer, radiation therapy, chemotherapy, immunotherapy, and chemoradiation therapy. However most of these methods are effective only in the early stage of disease and commonly lead to serious side effects on normal tissues and organs [20]. Hence, any preventive or suppressive approaches would be vital. Recently, studies have documented the remarkable ability of metallic nanoparticles especially silver nanoparticles to elicit cytotoxicity in cancer cells by mechanisms involving cell cycle arrest, DNA damage, apoptosis, or necrosis and generation of reactive oxygen species (ROS) and oxidative stress [18,21]. Silver NPs are also potent sensitizers for cancer and radiotherapy, and chemotherapy and show significant antitumor activity and toxicity in several animal models [22].

In the present work, leaf extract of *Teucrium polium* L., a medicinal plant which belongs to the *Lamiaceae* family was used as reducing as well as stabilizing agent/capping agent for biosynthesis of silver NPs to treatment of gastric cancer [23]. T. polium and other species belonging to the genus *Teucrium* have long been used for the treatment of diabetes, gastric inflammation, and convulsion in traditional medicine. It is also known for its anti-ulcer, anti-inflammatory, antibacterial, antispasmodic, antihypertensive, antinociceptive, anorexic and anticancer effects [24,25]. The alcoholic extract of T. polium inhibits proliferation and colonization of human carcinomas such as breast (BT20), prostate (DU145), lung (A549), and adenocarcinoma (MCF-7) cell lines [26]. The major phytochemical constituents present in T. polium plant is reported to contain diterpenoids, flavonoids, iridoids, sterols, and terpenoids, which can be responsible for the cytotoxic activity and antitumor properties [27]. In the present study, we used the leaf extract of T. polium plant for the eco-friendly synthesis of Ag NPs. The green synthesized nanoparticles were systematically characterized by UV−**V**is spectroscopy, X-ray diffraction (XRD), FTIR, and SEM microscopy methods. The cytotoxic activities of T. palium-AgNPs against human gastric cancer MNK45 cell line were also reported.

2. Materials and methods

2.1. Materials

Silver nitrate ($AgNO_3$) and potassium bromide (KBr) were purchased from Sigma-Aldrich (St. Louis, USA). MNK45 human gastric cancer cell line was obtained from pastor institute of Iran. The T. polium plant used in this study were collected from Kerman, Iran in June 2018.

2.2. Preparation of aqueous extract of T. polium

To prepare the T. polium leaf extract, the aerial parts of plant were washed thoroughly using double distilled water, dried completely in the shade and ground finely. Thereafter, 4.5 gr of T. polium powder was added to 50 ml of ultra-pure water and heated for 50 min at temperature of **70 °C** using water bath. After cooling to room temperature, the solution was filtered using Whatman No.1 filter paper and then centrifuged at 5000 rpm (Sigma 3-30 KS) for 10 min. The supernatant was then removed and stored at temperature of 4 °C and used for further experiments.

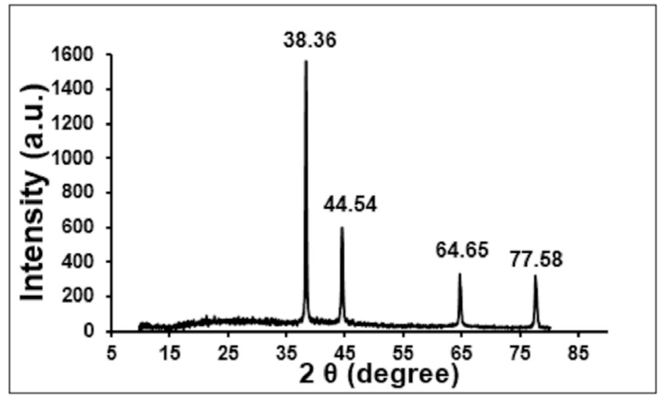

Fig. 1. XRD spectrum of AgNPs biosynthesized by T. polium aqueous extract.

2.3. Biosynthesis of silver nanoparticles

For bio-synthesize of silver nanoparticles, 10 ml of the prepared T. polium leaf extract was added to 90 mL of 1 mM silver nitrate ($AgNO_3$) aqueous solution and the mixture was continuously stirred for 30 min at room temperature. The bio-reduction of Ag^+ ions to Ag (0) and formation of the silver nanoparticles was monitored and determined through a change of appearance of the mixture that changed from transparent to dark brownish. The bio-reduced aqueous component was then characterized using UV−**V**is spectroscopy, XRD, FTIR, and SEM techniques.

2.4. Characterization of biosynthesized silver nanoparticles

2.4.1. XRD spectroscopy

The bio-reduced AgNPs were examined by XRD analyses to verify the crystal and nano-structural of Ag particles. The spectra were recorded in the scanning mode on a Philips X Pert-PRO PW3050/60 diffractometer employing Cu Kα radiations at 40 kV and 30 mA over the 2θ range of 10°-80°.

2.4.2. UV−Vis spectral analysis

The formation and optical properties of T. polium-AgNPs were studied by UV−Vis absorption spectrophotometer in the range between 380 and 800 nm. Picodrop spectrometer (P200 picodrop spectrophotometer, UK) instrument was used for measurements.

2.4.3. FTIR spectroscopy

FTIR analysis was used to identify and characterize biomolecules of T. polium plant extract involved in formation and stabilization of AgNPs. For this, purified T. polium-AgNPs in the form of powder were manually grinded with potassium bromide to make a pellet. The FTIR spectra were recorded at a wavelength of 400−4000 cm^{-1} using WQF-520 FT-IR spectrometer in the diffuse reflectance mode.

2.4.4. Microscopy study

Morphology, shape and particle size are the most important characteristics of NPs systems. They determine the biological fate, targeting ability, toxicity, and biodistribution of nanoparticle systems. In this study morphology, size and size distribution of the bio-synthesized AgNPs was analyzed using the images obtained with a field-emission scanning electron microscope (FE-SEM, model TE-SCAN MIRA3, operating voltage. 15 kV).

2.5. In vitro anticancer study

To check the potentiality of T. polium-AgNPs for biomedical

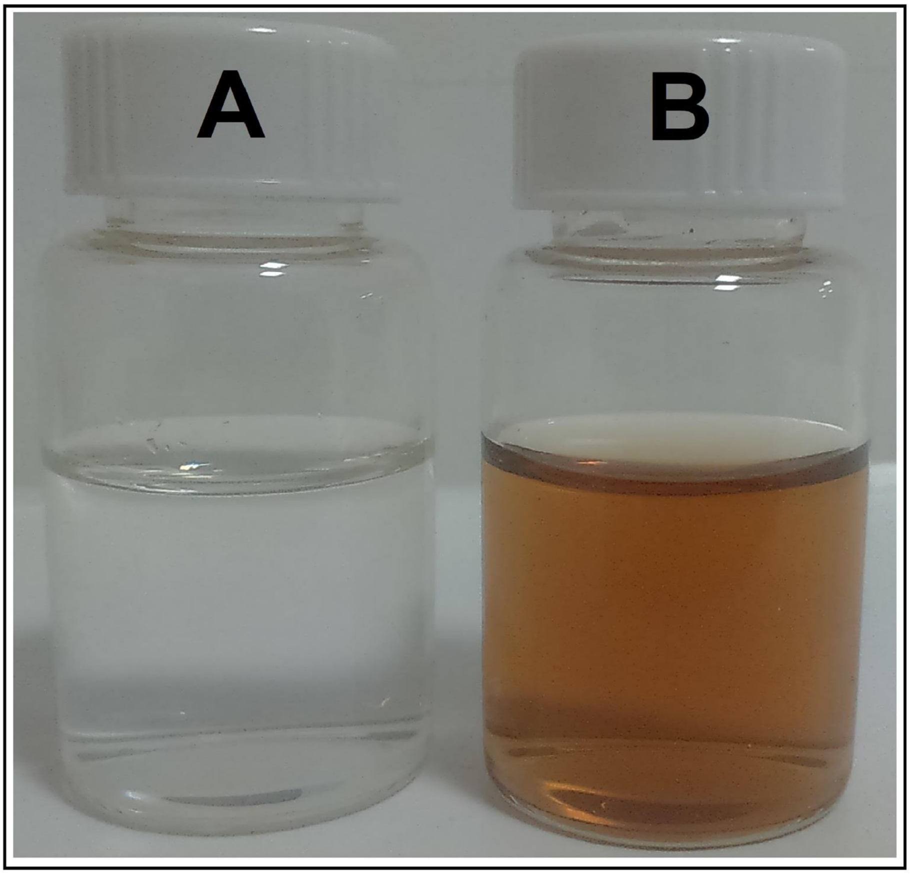

Fig. 2. Color change of T. polium extract treated with silver nitrate 24 h after treatment.

applications, we have checked the cytotoxicity of prepared nanoparticles towards MNK45 human gastric cancer cell line. The cytotoxicity assay on MNK45 cancer cells was evaluated by 3-(4,5-dimethylthiazol-2-yl) −2,5-diphenyltetrazolium (MTT) assay. Briefly, MNK45 cells were seeded at a density of 5×10^3 cells/ml in 96-well culture plates in high glucose Dulbecco's modified Eagle's medium (DMEM) containing 10% **fetal bovine serum (FBS)** in a humidified atmosphere of CO_2 (5%) at 37 °C temperature for about

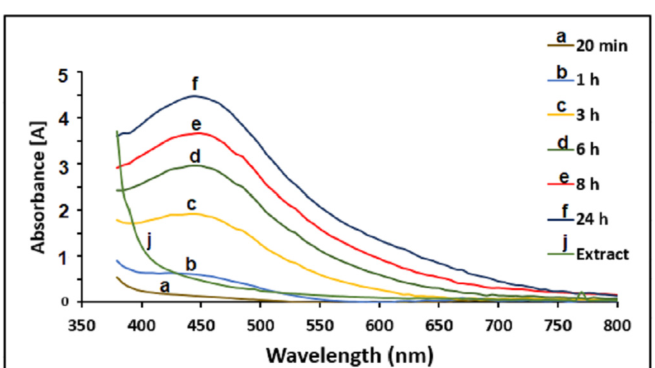

Fig. 3. UV−Vis absorption spectrum of aqueous silver nanoparticles synthesized by T. polium leaf extract and the incubation time is 24 h. (a) $AgNO_3$ 1 mM + T. polium extract, $\lambda_{max} = 434$ nm, 20 min, (b) $AgNO_3$ 1 mM + T. polium extract, $\lambda_{max} = 436$ nm, 1 h, (c) $AgNO_3$ 1 mM + T. polium extract, $\lambda_{max} = 439$ nm, 3 h, (d) $AgNO_3$ 1 mM + T. polium extract, $\lambda_{max} = 440$ nm, 6 h, (e) $AgNO_3$ 1 mM + T. polium extract, $\lambda_{max} = 438$ nm, 8 h, and (f) $AgNO_3$ 1 mM + T. polium extract, $\lambda_{max} = 439$ nm, 24 h, (j) T. polium extract.

24 h. After the incubation period, the media was discarded and dilutions of T. polium-AgNPs at different concentrations (0, 12.5, 25, 75 and 130 μg/ml) were added to each well and left for 48 h at 37 °C. Then, the media was discarded and 50 μl MTT reagent (0.5 mg/mL) were added to each well and incubated for 4 h in humidified CO_2 (5%) incubator. Thereafter, 100 μl of dimethyl**s**ulfoxide (DMSO) was added to each well to dissolve the formazan crystal formed by live cells. The optical absorbance of each well was then measured at 570 nm using a Cytation 5 cell **i**maging **m**ulti-**m**ode **r**eader from Bio Tek.

2.6. Statistical analysis

All experiments were performed in triplicate and the results were expressed as the mean ± standard deviation. The IC_{50} value (half maximal inhibitory concentration) was calculated by 4-parameter curve fitting using the Sigma Plot program (version 12, SPSS, Inc., Chicago).

3. Results and discussion

3.1. X-ray diffraction (XRD) analysis

The X-ray diffraction patterns of powder sample of T. polium-AgNPs have shown distinct diffraction peaks at 2θ angles of 38.36°, 44.54°, 64.65°, and 77.58° which can be indexed to the (111), (200), (220), and (311) Bragg's reflection of the **f**ace-centered **c**ubic (FCC) structure of silver crystal, respectively (Fig. 1). The results of XRD pattern of the T. polium-AgNPs showed that these products had pure crystalline structure.

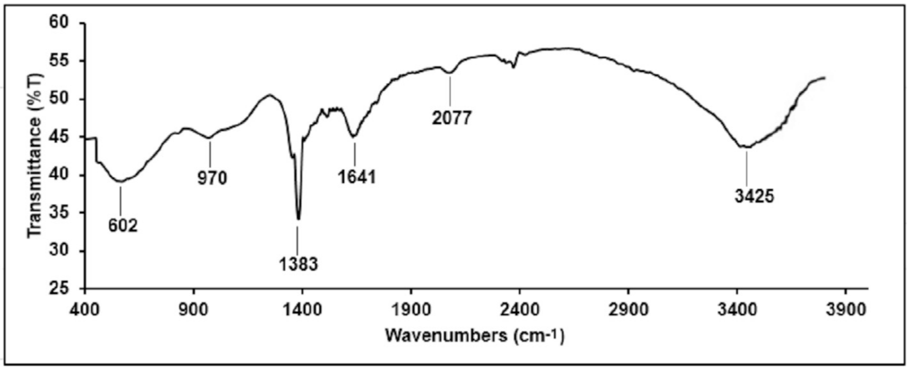

Fig. 4. Fourier transform-infrared spectroscopy spectrum of prepared T. polium-Ag NPs.

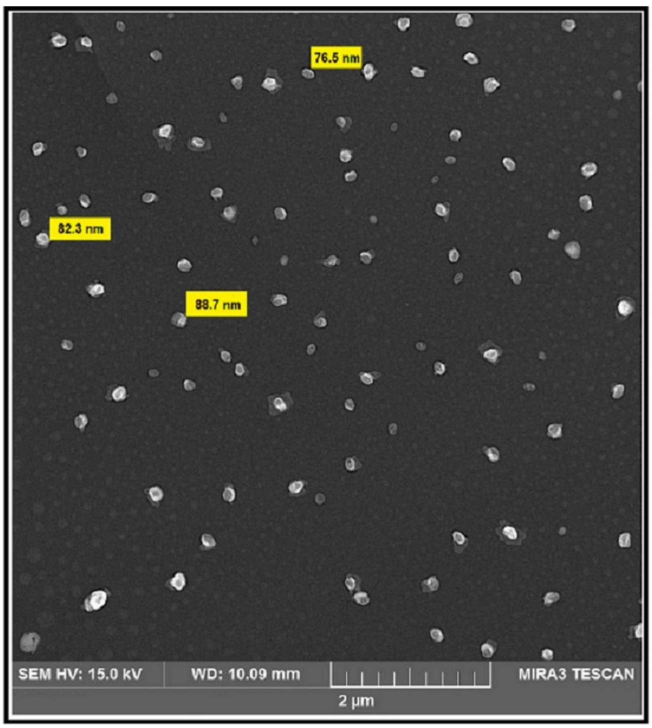

Fig. 5. FE-SEM image of silver nanoparticles synthesized from T. polium.

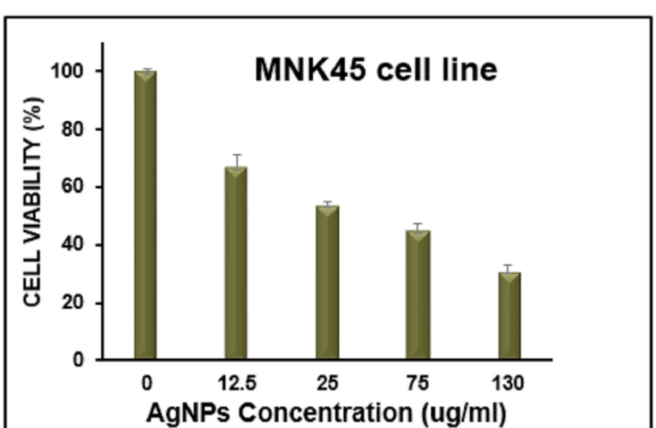

Fig. 6. In vitro viability of MNK45 gastric cancer cells incubated with different concentration of T. polium-AgNPs (12.5 μg/ml, 25 μg/ml, 75 μg/ml, 130 μg/ml).

3.2. Characterization of AgNPs by UV–Visible spectroscopy

One interesting properties of metal materials on the nanoscale is their optical properties which changes proportional to the size and shape of nanoparticles. In Fig. 2 the change in the color from clear to dark brown indicated the occurrence of a redox reaction whereby silver ions are reduced to silver nanoparticles by the plant components. The color change is due to the collective oscillation of free electrons in particles, phenomenon known as the surface plasmon resonance (SPR) with the AgNPs [28]. The SPR of the nanoparticles produced a peak centered at around λ_{max} ~434–440 nm indicating the reduction of silver nitrate into stable spherical silver nanoparticles (Fig. 3). The UV–**V**is spectrophotometer analysis also showed that, as the incubation time of $AgNO_3$ solution with the plant extract increases, the intensity of the absorbance were gradually increased which indicated that silver nanoparticles were continuously formed during the reaction.

3.3. FTIR analysis

The FT-IR spectroscopic studies were performed to identify the possible biomolecules in T. polium extract responsible for capping which leads to efficient stabilization of silver nanoparticles. As shown in Fig. 4, the broad and strong peak in 3425 cm^{-1} represent the O–H stretching vibration of polyphenolic compounds or flavonoids [10]. The absorption peaks emerged at 1641 and 1383 cm^{-1} correspond to amide I and II, respectively, arising due to carbonyl (C–O) stretch in proteins [10]. The peak at 970 cm^{-1} attributed to glycoside or ether (C–O–C) groups in T. polium-AgNPs [29]. FTIR results confirmed the participation of the bioactive compounds present in the T. polium extract like flavonoids and proteins in the bioreduction of silver nitrate and biosynthesis of AgNPs.

3.4. SEM morphology study

The shape and size distribution was conducted by EF-SEM images from T. polium-AgNPs colloidal solution (Fig. 5). The **FE**-SEM analysis revealed that most of the particles are spherical or near spherically shaped ranging from 70 to 100 nm in size. FE-SEM images showed individual NPs and were well polydispersed.

3.5. Anti-proliferative activity against cancer cell line

The cytotoxic effect of various concentrations of T. polium-AgNPs was assessed in MNK45 human gastric cancer cell cultures using MTT assay. Fig. 6 shows when the concentration of T. polium-AgNPs increased to 130 μg/ml, the cell viability of MNK45 gastric cancer cells reduced to 26.1%. The IC_{50} value of T. polium-AgNPs with MNK45 cancer cells was seen in 68.2 μg/ml after 48 h exposure. MTT assay results showed a dose-dependent decrease in MNK45 gastric cancer cell proliferation. It is clear that the treatment with 12.5, 25, 75 and 130 μl/ml of T. polium plant extract leads to a dose-dependent increase in cell death in MNK45 human cell line. Thus, this work clearly demonstrates that AgNPs synthesized from the T. polium aqueous extract provokes cell death in human MNK45. In the past decade, silver nanoparticles are increasingly being explored as tools for development of novel cancer therapeutics, due to their unique properties to enhance safety and potential therapeutic efficacy [30]. Several in vitro studies have indicated that silver nanoparticles can enter cells through endocytosis and localized in the perinuclear space of cytoplasm and endo-lysosomal compartment. Besides, silver nanoparticles can enter the mitochondria and disrupt mitochondrial respiratory chain and produce reactive oxygen species (ROS) [31]. ROS cause damage to proteins, lipids, nucleic acids, membranes and organelles, and in turn initiate expression of apoptotic genes and cell death [32]. In summary, the mechanisms of silver nanoparticles as toxic can lead to damage nucleic acids and organelles, oxidative stress, induction of apoptosis, and mitochondrial damage to cancer cells [31]. Several reports are available on the synthesis of silver nanoparticles from plants such as *Trapa natans* [18], *Alternanthera sessilis* [33], *Phoenix dactylifera* [34], *Artemisia turcomanica* [35], *Cleome viscosa* L. [36], *Lycium chinense* [37], *Artocarpus integer* [38], *Taxus baccata* [39], *Ecklonia cava* [40], *Clerodendrum phlomidis* [41] and their cytotoxicity on various cancer cells. Several medicinal plants contain large amount of antioxidants such as flavonoids, terpenes, phenolic acids, tocopherols and vitamin C, which provide protective effects against cardiovascular, neurodegenerative and cancer diseases [42,43]. Sreekanth et al. developed AgNPs from ***Saccharina japonica***, a brown algae and showed their high cytotoxic effect against human cervical adenocarcinoma cell line (HeLa). HeLa cells treated with these nanoparticles showed morphological changes and induction of apoptosis in cancer cells [44]. Saravanakumar et al. have reported the efficiency of green synthesized AgNPs using *Toxicodendron vernicifluum* (Tv) plant extract as a cytotoxic agent against human lung carcinoma cancer cell line (A549). Their results showed that, the Tv-AgNPs selectively targeted and damaged the lung cancer cells through ROS generation [45]. In another study by Pathak et al. they used fruit extract of *Scindapsus officinalis* to biosynthesise of silver nanoparticles as an antitumor agent against hepatocellular carcinoma cell line (HepG2) and human breast adenocarcinoma cell line (MCF-7). The results revealed bio-synthesized silver NPs possess high cytotoxic action against cancer cells [46]. The AgNPs **s**ynthesized by Prabhu et al. using ***Vitex negundo* L** aqueous extract showed a reduced cell viability in HCT15 human colon cancer cells by inducing apoptosis in cancer cells [47]. In our study, T. polium-AgNPs exhibited strong cytotoxic activity against MNK45 human gastric cancer cell line. The presence of different bioactive molecules in T. polium extract bond to silver NPs surface like amino acids, glycosides, flavonoids, and polyphenols as well as nano-sized silver particles can be responsible for anticancer activity of T. polium-AgNPs.

4. Conclusion

In the study aqueous extract of T. polium plant applied to green synthesis of silver nanoparticles and its anticancer activity tested. Due to the capping and reducing nature of the phytoconstituents in the T. polium extract, a cap was formed around the AgNPs, making them stable. Our study showed that T. polium-AgNPs exhibit anticancer effect on MNK45 human gastric cancer cell line. Our results suggest that, the biosynthesized silver NPs from T. polium are good alternatives in medicinal and therapeutic applications.

Author

All authors contributed equally to this work.

Declaration of competing interests

The author declares that there are no conflict of interests regarding the publication of this paper.

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